Adherence to healthy lifestyles and incidence of diabetes and mortality among individuals with diabetes: a systematic review and meta-analysis of prospective studies

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ABSTRACT

Introduction Lifestyle factors in combination have been hypothesised to be associated with the prevention of type 2 diabetes (T2D) and mortality among individuals with T2D. The aim was to conduct a systematic review and meta-analysis to quantify the association between lifestyle indices and incident T2D as well as mortality in individuals with T2D.

Methods PubMed and Web of Science were searched up to September 2019. We included prospective cohort studies investigating at least three lifestyle factors in association with T2D, or all-cause mortality in individuals with diabetes. We conducted pairwise and dose-response meta-analyses to calculate summary relative risks (SRR) by using random effects model.

Results In total, 19 studies were included. Adhering to a healthy lifestyle (mostly favourable diet, physical activity, non-smoking, moderate alcohol intake and normal weight) was associated with a reduced SRR of 78% for T2D (SRR: 0.22; 95% CI: 0.16 to 0.32; n=14) and 57% for mortality (SRR: 0.43; 95% CI: 0.31 to 0.58; n=5) compared with low adherence to a healthy lifestyle. In dose-response analyses, the adherence to every additional healthy lifestyle factor was associated with a reduced relative risk of 32% (95% CI: 28% to 36%) for T2D and 21% (95% CI: 15% to 26%) for mortality.

Conclusions Our findings underline the importance of the joint adherence to healthy lifestyle factors to prevent T2D and improve survival among individuals with diabetes. Adherence to every additional health lifestyle factor play a role in the T2D prevention and progression.

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INTRODUCTION

Since 2000, it has been estimated that the worldwide prevalence of diabetes in adults has risen from 4.6% to about 9%.1 5 In 2019, about 460 million people were estimated to live with diabetes and a further increase is projected.7 Type 2 diabetes (T2D) is accompanied by macrovascular and microvascular complications such as cardiovascular diseases, retinopathy and nephropathy, and consequently associated with increased premature death. Thus, it is a challenge to healthcare systems worldwide and a burden regarding reduced lifetime and quality of life among patients with T2D.7

Evidence exists that a healthy lifestyle, including maintaining a normal body weight, not smoking, being physically active, adhering to a healthy diet and drinking alcohol in a moderate range can prevent the incidence of T2D.8–16 Much of this knowledge on these associations is based on studies that have focused on each lifestyle factor separately, but lifestyle factors are strongly related to each other, and thus it is of strong interest to summarise the preventive combined impact of a healthy lifestyle factors regarding risk of T2D.17–20 Prospective studies focusing on lifestyle indices (a construct that accounts for simultaneous effects of single lifestyle factors) reported a decreased risk of T2D from 44% up to 94%4 9 for a healthy compared with an unhealthy lifestyle. The variation in findings could be explained by differences in associations between sex, geographic location and number or definition of components included in the lifestyle index. Moreover, although lifestyle modifications are included in diabetes management guidelines,10 evidence on the association of lifestyle factors regarding diabetes-related end points, including premature death, is less clear. There is indication for an association between the single lifestyle factors mentioned above and survival in individuals with T2D,11 12 and few prospective studies investigated the potential for risk reduction of all-cause mortality associated with adherence to a favourable lifestyle in individuals with T2D.13–15 These studies reported a decreased relative risk of mortality from 44%14 up to 72%.15

Recently, a meta-analysis summarised studies on the association between combined lifestyle factors and T2D as well as incident cardiovascular diseases and mortality in individuals with diabetes.16 However, the authors combined studies investigating lifestyle indices and cardiovascular risk markers such as blood pressure, blood lipids and blood glucose. These surrogate markers are influenced by lifestyle factors as well as genetic predisposition, and cannot be considered as lifestyle factors by itself. Moreover, three additional studies investigating lifestyle indices and incident T2D are available.17–19 Moreover, so far no dose-response meta-analysis has been carried out to summarise these findings.

Thus, we conducted a systematic review and meta-analysis of the association on the combined
impact of lifestyle factors and risk of T2D as well as all-cause mortality in individuals with T2D derived from prospective observational studies. We investigated strong versus low adherence to a healthy lifestyle, linear dose-response relation and evaluated the shape of the association by performing non-linear dose-response meta-analysis.

METHODS
Data sources and searches
The systematic literature search was carried out by two researchers independently. PubMed and Web of Science were searched from inception up to 17 September 2019. The full search strategy in PubMed is included in the online supplementary table A1. In addition, we searched the reference list of identified studies and relevant reviews for further relevant studies. We followed standard criteria provided by the meta-analysis of observational studies in epidemiology (MOOSE guidelines). The systematic review and meta-analysis was registered in PROSPERO International Prospective Register of Systematic Reviews.

Study selection
Studies were included if: i) they reported on the association between the combined effect of at least three lifestyle factors with risk of T2D, or all-cause mortality in individuals with T2D, respectively, ii) they were prospective, iii) provided effect estimates, reported as HR, relative risk (RR) or OR with the 95% CIs. We applied the following exclusion criteria: i) studies including cardiovascular markers in the index, ii) interaction studies, iii) case-control, cross-sectional and intervention studies, iv) reviews, conference abstracts, comments, v) studies investigating gestational diabetes.

When multiple reports were published from the same study, we included the most recent publication and the study with the largest number of cases (cases with new onset of T2D or cases of death, respectively) or the study including the highest number of lifestyle factors in our meta-analysis. A detailed list with excluded studies and the reason for exclusion is presented in the online supplementary table A2.

Data extraction and quality assessment
We extracted the following data: the first author’s last name, year of publication, country where the study was conducted, if available name of the study, duration of follow-up, age and sex of the participants at study entry, total sample size, number of cases, outcome (incidence of T2D or all-cause mortality among individuals with T2D), outcome assessment, included lifestyle factors, low-risk group of each lifestyle factor, risk estimate with corresponding 95% CI and confounders. One researcher extracted the data and another researcher double-checked for accuracy. We contacted authors to request additional information if needed.

Risk of bias was assessed using the Cochrane Risk of bias in Non-randomised Studies of Interventions (ROBINS-I) tool. The tool consists of the following seven domains: 1) confounding, 2) selection of participants, 3) measurement of the exposure, 4) misclassification of exposure during follow-up, 5) missing data, 6) measurement of outcomes and 7) selective reporting. A detailed description of judgement of potential risk of bias is given in the online supplementary table A3. Two researchers assessed the risk of bias independently. Any disagreements were resolved by consensus or by consultation of a third researcher.

Data synthesis and analysis
We conducted different types of analyses regarding the associations between healthy lifestyle and risk of T2D and mortality among individuals with T2D. First, we conducted pairwise meta-analysis by comparing high adherence to a healthy lifestyle with low adherence. Second, in dose-response meta-analysis we investigated the risk per one additional healthy lifestyle factor, and third, we evaluated the shape of the relation between the numbers of healthy lifestyle factors for both outcomes by using non-linear dose-response meta-analysis. Summary relative risks (SRR) and 95% CIs for healthy lifestyle were estimated using a random effects model. The average of the natural logarithm of the SRRs was estimated and the RR from each study was weighted using the method of moments by DerSimonian and Laird. For one study that reported RRs separately for men and women, we combined both RRs using a fixed effect model before entering in the RR into the overall meta-analysis. If an unhealthy lifestyle was not selected as reference category, risk estimates were converted by using the method of Hamling et al. If studies did not report on the linear association between lifestyle factors (increment per one additional factor) and the outcomes, we calculated the study-specific slopes and corresponding 95% CIs from the natural logarithm of the reported RRs and 95% CIs across the number of included lifestyle factor, using the method of Greenland and Longnecker.

For this analysis, any study that reported sufficient information required for the dose-response meta-analysis was included, regardless of the total number or the combination of lifestyle factors. In detail, this analysis requires the number of cases and total number of person-years per category, the mean exposure value with RRs and corresponding 95% CI of at least three categories. If the relevant data were not reported in the studies, the number of cases and person-years per category have been estimated as previously described. Finally, we evaluated a potential non-linear relation between the number of lifestyle factors and risk of T2D or all-cause mortality among individuals with T2D by using restricted cubic spline regression models described by Orsini et al. A likelihood ratio test was used to test for non-linearity. We calculated I² as a measure of inconsistency. Tau² and prediction intervals (PI) were estimated to investigate the between-study heterogeneity. The PI indicates that the underlying true effect size of future studies will lie with a certainty of 95% within this range. Furthermore, subgroup analyses were conducted to investigate sources of heterogeneity between the studies. Differences in sex, geographical area, duration of follow-up, number of cases, factors included in the lifestyle index and adjustment factors were tested using meta-regression.

Additionally, sensitivity analyses including studies with similar combinations of lifestyle factors as well as excluding studies with serious risk of bias were conducted.

If there are at least 10 studies available, we assessed publication bias and small study effects by using Egger’s test and by visual inspection of funnel plots. Potential publication bias was indicated by asymmetry of the funnel plot and a p value <0.1 for Egger’s test.

The statistical analyses were conducted using the software package Stata V.14.2 software (StataCorp, Texas, USA).

RESULTS
Out of 6888 articles, 126 full-text articles were screened and a total of 18 studies met the inclusion criteria (figure 1). One additional study was identified through the screening of reference lists. The characteristics of all included 19 studies are presented in the online supplementary tables A4 and A5. Fourteen studies investigated the association of lifestyle...
indices and incident T2D and five studies investigated all-cause mortality in individuals with T2D.\textsuperscript{13-15 39 40}

**Study characteristics**

Seven studies (nine cohorts)\textsuperscript{8 9 14 20 21 37 41} have been conducted in the USA, six in Europe,\textsuperscript{7 13 17 18 24 39} three in Asia,\textsuperscript{15 35 38} and one in Australia.\textsuperscript{34} In one study, 40 different countries were included.\textsuperscript{40} The follow-up time ranged from 2\textsuperscript{9} to 30 years.\textsuperscript{5 18} The number of healthy factors included in the studies ranged from three to seven. All studies included physical activity in their lifestyle index. Additionally, 18 studies included diet and smoking,\textsuperscript{7–9 13–15 17 18 20 21 24 34 35 37–41} 17 a measure of overweight/obesity,\textsuperscript{7 8 13 14 17 18 20 21 24 34–40} 12 alcohol consumption,\textsuperscript{8 9 13–15 17 18 20 21 24 34–40} 2 sleep duration or sleep-disordered breathing burden,\textsuperscript{38 41} 1 meal patterns,\textsuperscript{38} and 1 social network.\textsuperscript{40}

With regard to the assessment of risk of bias, 17 studies were assessed as having moderate and 2 studies as having serious risk of bias (online supplementary table A6).

**Figure 1** Flow chart of the study selection process. T2D, type 2 diabetes.

**Figure 2** Meta-analyses of lifestyle indices and incident type 2 diabetes. (A) High vs low adherence to a healthy lifestyle, (B) dose-response meta-analysis showing the summary risk ratio per one point increase in the healthy lifestyle index and (C) non-linear dose-response meta-analysis. RR, relative risk.

In the linear dose-response meta-analysis including data from 12 cohorts,\textsuperscript{7,8 13 14 17 18 20 21 24 34–38} the SRR for adherence to one additional healthy lifestyle behaviour regarding incidence of T2D was 0.68 (95% CI: 0.64 to 0.72, tau\textsuperscript{2}: 0.01; 95% PI: 0.55 to 0.84; I\textsuperscript{2}: 95.6%) (figure 2B). The test for non-linear dose-response was statistically significant indicating a higher reduction in the SRR for the first three healthy lifestyle factors than for four and more lifestyle factors (figure 2C). Adherence to one, two, three, four, five or six healthy factors was associated with a relative risk reduction of 28% (SRR: 0.72; 95% CI: 0.67 to 0.77), 49% (SRR: 0.51; 95% CI:
**Table 1** Pairwise meta-analysis for a healthy lifestyle and incidence of type 2 diabetes by subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No of cohorts</th>
<th>SRRs (95% CI)*</th>
<th>Tau²</th>
<th>I² (%)</th>
<th>P within subgroup †</th>
<th>P between subgroup ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>16</td>
<td>0.22 (0.16 to 0.32)</td>
<td>0.42</td>
<td>89.8</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>0.20 (0.12 to 0.31)</td>
<td>0.12</td>
<td>45.9</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
<td>0.13 (0.07 to 0.23)</td>
<td>0.44</td>
<td>87.5</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Men and women</td>
<td>8</td>
<td>0.30 (0.18 to 0.51)</td>
<td>0.50</td>
<td>88.7</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Geographic area</strong></td>
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<td></td>
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</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>0.27 (0.11 to 0.66)</td>
<td>0.31</td>
<td>76.0</td>
<td>0.04</td>
<td>0.92</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>0.19 (0.11 to 0.33)</td>
<td>0.23</td>
<td>84.5</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>USA</td>
<td>8</td>
<td>0.21 (0.10 to 0.41)</td>
<td>0.91</td>
<td>93.8</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Australia</td>
<td>2</td>
<td>0.30 (0.14 to 0.39)</td>
<td>0.00</td>
<td>0.0</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;10 years</td>
<td>8</td>
<td>0.32 (0.19 to 0.53)</td>
<td>0.49</td>
<td>88.8</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>≥10 years</td>
<td>8</td>
<td>0.15 (0.11 to 0.22)</td>
<td>0.15</td>
<td>77.5</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Number of cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>9</td>
<td>0.33 (0.20 to 0.55)</td>
<td>0.52</td>
<td>87.1</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>≥1000</td>
<td>7</td>
<td>0.14 (0.10 to 0.20)</td>
<td>0.13</td>
<td>78.1</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Body weight status included in lifestyle index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>0.19 (0.14 to 0.26)</td>
<td>0.26</td>
<td>84.3</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>0.66 (0.48 to 0.90)</td>
<td>0.00</td>
<td>0.0</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol included in lifestyle index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>0.19 (0.14 to 0.27)</td>
<td>0.25</td>
<td>84.1</td>
<td>&lt;0.001</td>
<td>0.26</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>0.31 (0.14 to 0.68)</td>
<td>0.74</td>
<td>92.6</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Sleep included in lifestyle index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>0.57 (0.34 to 0.94)</td>
<td>0.08</td>
<td>59.2</td>
<td>0.12</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>0.20 (0.14 to 0.27)</td>
<td>0.28</td>
<td>85.3</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Sedentary behaviour included in lifestyle index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>0.47 (0.20 to 1.09)</td>
<td>0.32</td>
<td>86.0</td>
<td>0.008</td>
<td>0.14</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>0.20 (0.14 to 0.28)</td>
<td>0.31</td>
<td>86.2</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adjustment for education</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>0.23 (0.15 to 0.35)</td>
<td>0.38</td>
<td>91.4</td>
<td>&lt;0.001</td>
<td>0.85</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>0.21 (0.10 to 0.46)</td>
<td>0.84</td>
<td>87.2</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td><strong>Adjustment for family history of diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>0.23 (0.16 to 0.33)</td>
<td>0.28</td>
<td>82.2</td>
<td>&lt;0.001</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>0.22 (0.09 to 0.53)</td>
<td>0.96</td>
<td>95.2</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
</tbody>
</table>

*SRRs were calculated using random effects models.
†P value for heterogeneity within subgroups.
‡P value for heterogeneity between subgroups estimated using meta-regression.
SRR, summary relative risk.

0.44 to 0.58), 66% (SRR: 0.34; 95% CI: 0.28 to 0.41), 78% (SRR: 0.22; 95% CI: 0.17 to 0.28), 87% (SRR: 0.13; 95% CI: 0.10 to 0.19), 92% (SRR: 0.08; 95% CI: 0.06 to 0.12) compared with low adherence to a healthy lifestyle.

Subgroup analyses with regard to sex, geographical area, length of follow-up and adjustment factors showed no differences between the groups (table 1). After stratification by the number of cases, a higher relative risk reduction was observed for studies including ≥1000 cases compared with <1000 cases. With regard to the lifestyle factors included in the indices, the SRR was reduced when combining studies (n=2) that did not included body weight status in the index (SRR: 0.66, 95%CI: 0.48 to 0.90) compared with studies that did (SRR: 0.19, 95%CI: 0.14 to 0.26, n=14). Excluding one study with serious risk of bias did not substantially change the results (SRR: 0.21; 95%CI: 0.15 to 0.30). Moreover, a sensitivity analysis including studies with similar combination of lifestyle factors was conducted. Most of the studies included physical activity, diet, body weight, smoking and alcohol (n=9) and the subgroup analysis showed similar results (SRR: 0.16, 95%CI: 0.11 to 0.21, I²: 75.9%, tau²: 0.14) compared with the overall summary effect estimate. There was no indication for potential publication bias or small study effects (p=0.36 from Egger’s test, online supplementary figure A1).

Lifestyle indices and all-cause mortality in individuals with type 2 diabetes

In total, 17 155 participants with T2D including 2115 cases of death were included in the present meta-analysis.13–15 39 40 The SRR for all-cause mortality was 0.43 (95% CI: 0.31 to 0.58; tau²: 0.08; 95% PI: 0.15 to 1.20; I²: 65.9%) comparing high
with low adherence to a healthy lifestyle (figure 3A). In the linear dose-response meta-analysis, one point increase in the healthy lifestyle index was associated with a SRR of 0.79 (95% CI: 0.72 to 0.85, tau²: 0.00, 95% PI: 0.62 to 1.02, I²: 69.9%) (figure 3B). There was no indication for non-linearity for the association between the lifestyle index and all-cause mortality among individuals with T2D (p=0.98, figure 3C). Adherence to one, two, three or four healthy lifestyle factors was associated with a relative risk reduction of mortality by 22% (SRR: 0.78; 95% CI: 0.72 to 0.85), 39% (SRR: 0.61; 95% CI: 0.53 to 0.71), 52% (SRR: 0.48; 95% CI: 0.39 to 0.58) and 62% (SRR: 0.38; 95% CI: 0.28 to 0.49) compared with low adherence to a healthy lifestyle. Excluding one study with serious risk of bias did not substantially change the results (SRR: 0.46, 95% CI: 0.33 to 0.66).

**DISCUSSION**

The present meta-analysis showed that adherence to a healthy lifestyle including a favourable diet, being physically active, non-smoking, a normal weight and low-to-moderate alcohol intake, was associated with reduced SRR of T2D by 78% and reduced SRR of all-cause mortality in individuals with T2D by 57% compared with individuals adhering to none or only one healthy lifestyle behaviour. The results of our meta-analysis are in accordance with previous meta-analyses showing that the combined effect of healthy lifestyle factors is associated with a reduced SRR in cardiovascular diseases by 66% and with a reduction of SRR by 66% in all-cause mortality among the general population.

This holistic approach might better capture the overall risk of different lifestyle factors.

The present meta-analysis is based on prospective cohort studies and the results are in agreement with intervention studies that investigated the combined effect of a healthy diet, physical activity and a reduction in body weight. In two diabetes prevention studies, participants were randomly assigned to an intervention group with the goals to reduce body weight, intake of total and saturated fat and increase fibre intake and physical activity. The cumulative incidence of T2D in the intervention group was 58% lower compared with the control group in both studies. In comparison to these interventions, the prospective studies included in the present meta-analysis were able to focus on more lifestyle factors such as smoking, alcohol intake and sleep duration. Some studies also investigated the population attributable fraction (PAF) or population attributable risk (PAR) of T2D that might have been prevented by a healthy lifestyle. These PAFs ranged from 34.4% (95% CI: 27.9% to 42.4%) to 89% (95% CI: 23% to 99%). Lv et al showed that almost three-quarters (PAR%: 72.6; 95% CI: 64.2% to 79.3%) of T2D cases might have been prevented by a favourable diet, being physically active, maintaining a normal weight, consuming low-to-moderate amount of alcohol and non-smoking. Interestingly, non-smoking and alcohol consumption added only little to the PAF in this study.

Our analysis indicated high statistically heterogeneity between the studies. In the sensitivity analysis, the association was stronger when combining studies with a larger number of cases compared with studies including less, and heterogeneity expressed as tau² was reduced. Slightly differences were observed for the subgroup meta-analyses regarding stratification by follow-up time and the inclusion of sleep duration in the lifestyle index. Studies with a follow-up ≥10 years showed a lower incidence of T2D (high vs low adherence to a healthy lifestyle) than studies with a follow-up duration <10 years, which might indicate that a long-term healthy lifestyle has more impact on the incidence of T2D. The follow-up time of the prospective studies varied from 2 to 30 years. As most of the included studies provided data on lifestyle factors only measured at baseline, we were not able to investigate changes over time. In our risk of bias evaluation, the lack of repeated measurements was taken into account and most studies were rated as moderate risk of bias as repeated measurements of the lifestyle factors were not available. Only two studies considered repeated measurements. Thus, lifestyle factors, such as diet and physical activity, could have changed during the follow-up, which may have influenced the results. Furthermore, in studies that included sleep duration in the lifestyle index,
the effect estimate was attenuated (compared with our main findings, and with studies that did not include sleep duration). However, only two studies investigated sleep duration and findings should be interpreted with caution. We found no other relevant differences in our subgroup analyses, suggesting that other factors might explain the observed heterogeneity between the studies. A possible explanation could be the different definitions of the lifestyle factors as well as indices. So far, there is no common lifestyle index available. The assessment, definition of single lifestyle factors as well as the different combinations of lifestyle factors included in the index may have influenced the results. Most lifestyle factors have been assessed by self-reports, and only for body weight status an objective measurement was available. Especially the assessment of diet in large cohort studies is challenging as instruments such as the food frequency questionnaire represents the whole diet of participants within a certain time period, but is prone to measurement errors. On the other side, instruments with less measurement errors such as food records or 24 hours dietary recalls represent the diet for a few days only and repeated assessment impose a high burden for study participants. In most studies, diet was assessed by a food frequency questionnaire, in one by a diet history, in another by a 24-hour food diary and in two studies it was not specified. In the risk of bias evaluation of each study, we accounted for the bias of exposure assessment, and most studies were rated as only moderate risk of bias due to the use of at least one non-validated instrument. Moreover, the definition of a healthy behaviour varied between studies. Whereas some studies included a dietary pattern, other studies focused only on single food groups such as fruit and vegetable consumption. The inclusion of the whole diet would be the preferred method to investigate diet with regard to T2D prevention. With regard to physical activity, many studies categorised at least 30 min exercise as healthy behaviour whereas another study only had information that individuals often or sometimes do physical exercise. These categorisations could result in misclassification of individuals and thus, also have an impact on the effect size and heterogeneity between studies. In the present meta-analysis, lifestyle factors such as sleeping duration, meal patterns or social behaviour, assessed by the size of the individual social network, were rarely included in the lifestyle indices. No study including a measure of sedentary behaviour was found. A recent meta-analysis showed that sedentary behaviour measured by TV watching was associated with incident T2D. In addition, another meta-analysis showed that sleep duration below 7 and above 8 hours is associated with an increased relative risk of T2D. Investigating these factors additionally to the other healthy lifestyle factors might also add important information to the overall impact of a healthy lifestyle for the prevention of T2D or all-cause mortality in individuals with T2D. Adherence to every additional healthy lifestyle factor play a role in the prevention and progression of T2D.

Strengths of the present meta-analysis include the large sample size (almost 900,000 participants) and the high number of T2D cases (>45,000). We included only prospective studies to avoid recall bias. Moreover, the advantage of observational studies is that lifestyle factors such as smoking and alcohol consumption could be investigated and that the studies exhibited a long follow-up. For lifestyle indices and incident T2D, we were able to conduct several subgroup analyses, indicating that the results may not be limited to specific study populations or characteristics. With regard to the limitations, the studies included in the meta-analysis were rated to be at moderate or serious risk of bias. However, this was especially due to potential residual confounding, which is a general limitation in observational studies. Another limitation is the measurement of lifestyle risk factors, which was conducted only at baseline, and relied on self-reports of lifestyle factors. Moreover, the definition of the lifestyle indices varied between the studies and dichotomising the lifestyle factors results in loss of information. However, although the definition of lifestyle indices varied between studies, consistent inverse associations of almost all studies underline the large relevance of adopting a healthy lifestyle.

In conclusion, adherence to a healthy lifestyle characterised by a favourable diet, non-smoking, being physically active and a normal body weight might be important for the prevention of T2D and all-cause mortality in individuals with T2D. Adherence to every additional healthy lifestyle factor play a role in the prevention and progression of T2D.

What is already known on this subject

► Single lifestyle factors are associated with the prevention of type 2 diabetes and all-cause mortality among individuals with type 2 diabetes.
► Lifestyle factors are strongly related to each other, and thus, the investigation of lifestyle indices rather than single lifestyle factors may be more advantageous to account for interrelations between lifestyle factors and is of strong public health interest.

What this study adds

► In our meta-analysis, adhering to a healthy lifestyle, including a favourable diet, physical activity, non-smoking, moderate alcohol intake and normal weight, was associated with a 78% reduced relative risk for type 2 diabetes and adherence to every additional healthy lifestyle factor was associated with a reduced relative risk of type 2 diabetes by 32%.
► For individuals with type 2 diabetes, the relative risk of all-cause mortality was reduced by 57% by comparing adherence to a healthy lifestyle versus non-adherence, and by 21% for adherence to every additional healthy lifestyle factor.
► Our findings underline the importance of the joint adherence to a healthy lifestyle—to prevent type 2 diabetes and improve survival among individuals with type 2 diabetes.

Contributors SS and JB designed the study question, conducted the literature screening, conducted the analyses and wrote the first draft of the paper. AB, MN and JB extracted the data. MN and JB assessed the risk of bias of included studies. SS and JB taking responsibility for the contents of the article. SS, MN, AB, UN and JB interpreted the data, critically reviewed the manuscript and approved submission of the final manuscript.

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